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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,546	09/29/2003	Masato Some	Q77645	7516

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	**PAPER NUMBER**
1631	

MAIL DATE	DELIVERY MODE
10/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,546	SOME ET AL.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/15/2007 has been entered.

CLAIMS UNDER EXAMINATION

Claims herein under examination are Claims 1, 2, 5, and 6. It is noted that claims 3, 4, 7, and 8 have been cancelled, as indicated in the remarks [p.1]. However, the amended claims filed 08/15/2007 do not consist of a complete claim set, as claims 7 and 8 are missing. Applicant is required to submit a complete claims set with correct claim status for each claim in response to this office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

PRIORITY

Acknowledgement of foreign priority to JAPAN 285102/2002, filed 9/30/2002, is granted.

DRAWINGS

The replacement drawings filed 09/20/2006 are not acceptable. The drawings again are objected to under 37 CFR 1.83(a) because they fail to show any type of units that identifies the nature of the data on the "x axis" and "y axis." Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

CLAIM REJECTIONS - 35 USC § 101

The rejection of claims 1, 2, 5, and 6 under 35 U.S.C. 101 because these claims were drawn to non-statutory subject matter is hereby withdrawn in view of applicant's amendments to claims 1 and 5.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step i) recites "indicating data x and y concerning expression quantities,..., respectively, with points plotted on a logarithmic coordinate system." As data is typically represented on coordinate systems using an x-axis (horizontal) and a y-axis (vertical), it is unclear whether "respectively" is intended to mean data x and data y are represented on two separate graphs or the same graph. Clarification is requested.

Claim 1: It is unclear as to the intended meaning of "concerning expression quantities." Clarification is requested.

Claim 1, step ii) recites the step of "calculating a coefficient 10^a from a value of an intercept "a" of an approximate straight line." As the coefficient 10^a is simply 10 raised to the power of "a", and therefore already contains the value "a", it is unclear in what way this coefficient is "calculated from a value of an intercept "a." Clarification is requested via clearer claim language.

Claim 1, step ii) recites the equation "log y = log x + a." As "a" was previously described as an "intercept of an approximate straight line", it is unclear whether the above equation is intended to represent an approximate straight line obtained from x and y data sets, a function

describing all input data, or a relationship between both x and y data sets and an error. Clarification is requested via clearer claim language.

Claim 5, step i) recites the phrase "respectively the data related to the second sample being on the vertical axis." It is unclear what limitation is intended by this phrase as it pertains to the first sample. It appears that the second sample data is limited to points along the vertical axis only. Clarification is requested via clearer claim language.

NEW MATTER

Claims 1, 3, 5, and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 1 has been amended to recite "indicating data x and y concerning expression quantities." In the response filed 08/15/2007, applicant does not point to support for the newly recited limitations. The Examiner has not found support for these limitations in the specification, and these limitations are not present within the scope of the original claims as filed. As the newly recited limitations are not supported by the originally filed claims or disclosure, the claims are rejected for reciting new matter. This rejection is necessitated by amendment.

Claim 5 has been amended to recite "plotting a logarithmic graph of data x and y related to a first sample versus data related to a second sample." In the response filed 08/15/2007, applicant does not point to support for the newly recited limitations. The Examiner has not found support for these limitations in the specification, and these limitations are not present

within the scope of the original claims as filed. As the newly recited limitations are not supported by the originally filed claims or disclosure, the claims are rejected for reciting new matter. This rejection is necessitated by amendment.

PRIOR ART REJECTION OF INDEFINITE CLAIMS

In view of the indefiniteness and lack of clarity in the instant claims, as set forth in the 35 USC 112 2nd rejections above, the Examiner has had difficulty in properly interpreting instant claims. However, to avoid piecemeal prosecution and to give applicant a better appreciation for relevant prior art if the claims are redrafted to avoid the 35 USC 112 2nd rejections, the Examiner has broadly interpreted the claims for purposes of applying the following prior art rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quackenbush (Nature Reviews Genetics, June 2001, Vol. 2, p. 418-427), in view of GRAPHING WITH LOGARITHMIC PAPER (Department of Physics, University of Guelph, http://www.physics.uoguelph.ca/tutorials/GLP, Published Oct. 1997, p. 1-5)

The instant claims are now directed to a method of normalizing gene expression data comprising steps of: indicating data x and y concerning expression quantities (i.e. gene expression data) with plots on a logarithmic coordinate system; calculating a coefficient 10^a from a value of an intercept "a" of an approximate straight line with slope = 1; performing division processing for dividing data of the second sample by the coefficient, whereby data for the second sample are normalized as y'; and outputting the result y'. Applicant's arguments that the Examiner has ignored key mathematical relationships in claims 1 and 5 that distinguish the present invention from the teachings of the prior art have been fully considered but are moot in view of the new grounds of rejections.

Quackenbush teaches a variety methods for normalizing gene expression data in order to adjust the data to compensate for experimental variability and to 'balance' the fluorescence signals from two samples. Specific methods include the determination of a normalization factor that is used to re-scale the gene expression data and the calculation of slopes and adjusting data so the slope = 1 [p.419, Box 1]. Furthermore, Quackenbush teaches steps for collecting samples from cells with different phenotypes (i.e. normal and diseased cells) [p.419, Col. 2, ¶5]; indicating data from two samples as a histogram representing the distribution of log2(ratio) values for a Cy5 intensity (vertical axis) and Cy3 intensity (horizontal axis; providing equations

relating y, x, and a coefficient and calculating the coefficient (i.e. slope) [Fig. 2c and 2d]; normalizing gene expression data and representing in scatter plots before (red) and after (blue) normalization of the measured intensities and log(intensities) also illustrate the transformation of the data [Fig. 2c and 2d], as in claims 1, 2, 5, and 6.

Quackenbush do not specifically teach the equation "log y = log x + a" or dividing data by the coefficient 10^a to normalize the data for the second sample where $y' = y/10^a$, as in claims 1 and 5, but do clearly teach the normalization of data (i.e. division processing), representation of data on a logarithmic scale, and linear interpolation of data, which is suggestive of the above limitations and equations.

GRAPHING WITH LOGARITHMIC PAPER (GLP) teaches methods for graphing data from two separate sources on a logarithmic scale (log-log graphs) [p.4, panel 10]. GLP also teaches equations of the form "log y = log a + b log x" [p.4, panel 9], and methods for re-calculating the coefficients to account for changes in the slope as well as x- and y-intercepts when the data is shifted from the origin [p.4 and 5]. Given the equation represented shifted data, as in claims 1 and 5, and a second line wherein data is not shifted from the origin, log y' = log x, simple mathematical manipulations using well-known laws of logarithms where slope and b = 1 yield the equation $y' = y/10^a$. Using the known techniques of GLP, one of ordinary skill in the art could determine the intercept "a", and thereby determine the coefficient 10^a and the re-scaled data point y'. Therefore, the Examiner considers the equations recite in claims 1 and 5 to be obvious variations of known logarithmic relationships and invites the applicant to demonstrate the novel or unobvious difference between the use of such formulas and calculations as disclosed in the prior art.

Therefore, as methods for normalizing and re-scaling data sets are well known and understood, it would be obvious to one of ordinary skill in the art at the time of the invention to

practice the known methods for normalizing gene expression data, as taught by Quackenbush above, using the known logarithmic equations for dealing with shifts in the logarithmic data sets, as taught by GLP above, since it would have been a mere use of common sense by one of ordinary skill in the art to normalize data by division processing using the above methods with no change in respective functionality for comparing samples concerning shifted gene expression data obtained from cells, resulting in the practice of the instantly claimed invention with predictable results. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (US Pat. No. 6,571,005; Filed Apr. 21, 2000), in view of in view of Stark et al. (US 5,568,400; Issued Oct. 22, 1996) and GRAPHING WITH LOGARITHMIC PAPER (Department of Physics, University of Guelph, http://www.physics.uoguelph.ca/tutorials/GLP, Published Oct. 1997, p. 1-5).

As set forth in the previous office action, Li et al. teach a method for comparing a first gene expression array to a second gene expression array. In particular, Li teaches the following aspects of the instantly claimed invention:

- Indicating gene expression data on a coordinate system from baseline and experimental array samples (i.e. normal and abnormal cells) (Fig. 2), which correlates to instant claims 1 step (i), 2, and 6.
- Calculating the slope of a low intensity region and high intensity region (Fig. 2) and (19), which correlates to calculation of a coefficient as in instant claim 1 step (ii). Note:

Calculation of the slope of a line (i.e. "$\Delta y/\Delta x$") can be achieved given any two points on line, including an x or y intercept.

- Relating intensities between two or more arrays as a straight line with a zero y-intercept (i.e. slope = 1) and multiplication by a scaling factor (slope of the line) to make the mean of the "experiment" chip the same as that of the baseline chip (17), which correlates to instant claim 1, step (ii).
- Performing division processing where intensity of each EST on an array was divided by the mean intensities of all ESTs on that array and multiplied by a nominal average intensity value (Col. 3, lines 11-23), which is a teaching for performing a division as in instant claims 1 and 5.

Li et al. do not specifically teach plotting logarithmic graphs of data, the equation "log y = log x + a" or dividing data by the coefficient 10^a to normalize the data for the second sample where $y' = y/10^a$, as in claims 1 and 5, but do clearly teach the normalization of data (i.e. division processing), representation of data on a logarithmic scale, and linear interpolation of data, which is suggestive of the above limitations and equations.

GRAPHING WITH LOGARITHMIC PAPER (GLP) teaches methods for graphing (i.e. outputting) data from two separate sources on a logarithmic scale (log-log graphs) [p.4, panel 10]. GLP also teaches equations of the form "log y = log a + b log x" [p.4, panel 9], and methods for re-calculating the coefficients to account for changes in the slope as well as x- and y-intercepts when the data is shifted from the origin [p.4 and 5]. For reasons set forth above, the Examiner considers the equations recite in claims 1 and 5 to be obvious variations of known logarithmic relationships and invites the applicant to demonstrate the novel or unobvious difference between the use of such formulas and calculations as disclosed in the prior art.

Stark teaches an improved method for processing spectral data to remove undesired variations in such data and to remove interfering information present in the data or corrects multiplicative effects present in the spectral data [Abstract]. In one aspect of the method, coefficients for a selected model are applied to the input spectral data based on reference spectra. The spectral data are then corrected based on the estimated coefficients for producing a linear additive structure for use in calibration, validation and determination by linear multivariate analysis. Therefore, Stark clearly provides evidence that one of ordinary skill in the art would be able to calculate coefficients and use said coefficients to normalize spectra data with predictable results. The method will improve the accuracy of spectral data structures derived from measurements using spectroscopy, image analysis, and other analytical technologies producing data of similar multivariate nature. [Abstract].

Therefore, it would be obvious to one of ordinary skill in the art at the time of the invention to practice the known methods for normalizing gene expression data, as taught by Li et al. above, using the known logarithmic equations taught by GLP, as it is well known that comparison of gene expression data is enhanced when the results of experiments are normalized to a single scale, as suggested by Li et al (Col. 3, lines 1-10). One of ordinary skill in the art would therefore have been motivated to normalize logarithmic data using calculated coefficients and logarithmic equations as set forth above for purposes of improving the accuracy of spectral data, resulting in the practice of the instantly claimed invention with predictable results, as suggested by GLP and Starks. For these reasons, the instant claims do not recite any new element or new function or unpredictable result.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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